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Nephrotoxicity of several newer agents

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The purpose of this brief communication is to review several drugs implicated as nephrotoxins in the recent literature. This review will not endeavor to provide an exhaustive review of all nephrotoxins. There are several excellent and comprehensive reviews of this topic available [1].

INCIDENCE OF ACUTE RENAL FAILURE CAUSED BY DRUGS

There is widespread agreement that drug nephrotoxicity plays a major role in the high incidence and prevalence of acute renal failure in both hospitalized and nonhospitalized patients. Recent reviews have suggested that between 5% and 10% of acute renal failure recognized in such patients is caused, at least in part, by drugs [2]. Antibiotics play a major role in these nephrotoxicities, but other drugs are clearly implicated in many cases. The incidence of acute renal failure caused by nephrotoxic agents is particularly notable among the elderly, and there are several reasons for this: (*1*) there is an age-related decline in glomerular filtration rate in older individuals, and this leads to a decreased clearance of primary drugs or the metabolites of such drugs; (*2*) there may be a decrease in kidney blood flow and an increase in concentration of some drugs in the cells of medulla; (*3*) primary differences exist between the elderly and nonelderly and pharmacokinetics of drugs. For example, there may be an increase in free-drug concentration in the elderly in conjunction with hypoalbuminemia, or because of retained metabolites [2]; (*4*) a decrease in total body water may also alter drug distribution in an adverse way; (*5*) finally, there may also be a decrease in hepatic metabolism with longer half-lives of some drugs. For example, in a recent study by Dowling et al, individuals with underlying renal disease had a decrease in the maximum cytochrome P450 enzyme activity inducible by rifampin as compared to normal controls [3].

With regard to the fate of individuals who develop acute renal failure caused by nephrotoxicity, several outcomes have been reported. In most cases, the drug nephrotoxicity is partly or wholly reversible. However, some authors have suggested that as many as 50% to 60% of individuals who suffer such nephrotoxicity may retain an element of permanent renal damage. One recent report suggested that individuals who have interstitial nephritis with granuloma formation on kidney biopsy are more vulnerable to developing these chronic kidney effects [4]. In this report, as many as 50% of subjects suffering from nephrotoxic acute renal failure suffered chronic and permanent renal damage from the exposure [4]. As with all cases of acute renal failure, the mortality rate is extremely high in hospitalized patients, and this is particularly true in the setting of the intensive care unit [5]. Thus, avoiding any decrement in kidney function caused by drug exposures is a major factor in reducing overall morbidity.

NEPHROTOXICITY CAUSED BY COX-2 INHIBITORS

The COX-2 drugs act by inhibiting the cyclooxygenase-2 isoenzyme, which is responsible for prostaglandin synthesis and is constitutive in some tissues. The enzyme is markedly stimulated by endotoxin, cytokines, and other growth factors. The well-known acute vasoconstriction that follows the inhibition of nonconstitutive prostaglandin synthesis in the kidney by nonselective cyclooxygenase inhibitors would theoretically be diminished by using a selective cyclooxygenase inhibitor. However, if arachidonate metabolism via COX were blocked, it might proceed down the lipooxygenase pathway, which could result in the production of vasoconstrictive leukotrienes, thereby leading to renal ischemia [6]. Additionally, COX-2 inhibitors may promote apoptosis in medullary interstitial cells under conditions of water deprivation, and this may also favor an acute reduction in kidney function [7].

There are several recent studies that have suggested that, under conditions of volume challenge, renal vasoconstriction does occur upon exposure to cyclooxygenase-2 inhibitors. One of these studies in humans suggested that there was as much as a 10 mL/minute decrease in glomerular filtration rate from baseline on day 6 of exposure to a selective cyclooxygenase inhibitor

[8]. Thus, the acute effects of exposure to such drugs may produce a decline in glomerular filtration rate (GFR) under certain circumstances. Other physiologic effects of the COX-2 isoenzyme in the kidney include inhibition of renin secretion stimulated via the macula densa [9], an effect to increase blood pressure in laboratory animals [10], and an ability to facilitate the natriuretic response to furosemide in laboratory animals [11]. The array of effects of inhibition of the COX-2 isoenzyme, then, might be a decrease in GFR, an increase in blood pressure and edema, a decrease in sodium excretion in response to loop diuretics, and hyperkalemia secondary to the antirenin effects of the drugs. The chronic effects of use of these drugs on kidney function is not known because the time of exposure to these drugs has been only in recent years.

Perhaps one of the most illuminating studies performed on the question of how common nephrotoxicity is in the setting of cyclooxygenase-2 inhibitors was from a study that was not designed to examine this question [12]. This study was aimed at learning the effect of celecoxib (200 mg bid) versus diclofenac and omeprazole on GI bleeding in arthritis patients; a 6-month follow-up was done in 2 groups of rheumatoid arthritis patients. The incidence of GI bleeding in the 2 groups was comparable at the end of 6 months. Of interest is the fact that hypertension, peripheral edema, and renal failure were noted in 24% of the celecoxib group and 31% of the diclofenac/omeprazole group. Renal failure was seen in 5.6% of the 144 celecoxib patients and 6.3% of the diclofenac plus omeprazole patients. Thus, it is clear that renal adverse events are common with the use of selective cyclooxygenase-2 inhibitors over relatively short periods of time. This leads to the conclusion that, for the time being, cyclooxygenase-2 inhibitors should not be characterized as "renal-protective." Cautions that are operant in the use of nonselective cyclooxygenase inhibitors should also be applied to these cyclooxygenase-2 inhibitors.

BISPHOSHONATES

The class of drugs known as bisphoshonates has been extremely useful as chronic therapy for not only hypercalcemia, but also in preventing fractures in patients with metastatic cancer. These drugs reduce morbidity from hypercalcemia, and also improve osteoporosis in this patient population group. The drugs work by binding phosphate crystals within the bone matrix, thereby disrupting osteolytic activity. In addition to being used in hypercalcemic syndromes in individuals with osteolytic metastases, these drugs are also useful in Paget's disease.

With regard to nephrotoxicity, there are a growing number of case reports of nephrotoxicity following use of pamidronate and zoledronate. With regard to pamidronate, the dose range of 90 to 360 mg/month for between 15 to 48 months has generated a number of these case reports. One interesting feature of pamidronate nephrotoxicity has been that in several individuals nephrotic syndrome with a collapsing glomerular sclerosis has been seen on renal biopsy [13]. There are also tubular atrophy, a loss of the proximal tubule brush border membrane, and cytoplasmic vacuolization as common features in this form of nephrotoxicity. Typically, there is very little complement staining and light IgM staining on immunofluorescence. Once the drug is stopped, there is frequently a slow resolution of the acute renal failure over several months. The mechanism of this nephrotoxicity is not completely understood, but involves the transport of pamidronate intracellularly in podocytes in all likelihood. The intracellular location of pamidronate inhibits mevalonate pathways and disrupts GTPase anchoring proteins. This, in turn, impairs cell energetics and compromises the cell skeleton. Prevention of pamidronate nephrotoxicity is best achieved by avoiding greater than 90 mg per month infusions and employing very slow IV infusions.

With regard to zoledronate, the incidence of acute renal failure has been reported to be in the 9% to 13% range (when 4 mg IV over 15 minutes every 3 to 4 weeks for 1 year has been given) [14]. The pathology of zoledronate nephrotoxicity is dominated by a diffuse tubular atrophy and injury without interstitial nephritis. The excretion of zoledronate is greater than the GFR, which suggests that there is active tubular secretion of the drug. The average time for developing the nephrotoxicity occurs at about the 5-month mark in most series. There is typically a gradual increase in the serum creatinine concentration, and slow recovery is expected. The avoidance of nephrotoxicity is best obtained by giving very slow infusions over 30 minutes to 40 minutes (and not 10 to 15 minutes). Volume repletion is also recommended before the drug is started.

INTRAVENOUS IMMUNOGLOBULIN G

Intravenous immunoglobulin G is useful in immunodeficiency syndromes where the total dose is 0.6 g/kg. Inflammatory neurologic conditions and myasthenia gravis along with blistering skin diseases are other indications for the drug. The adverse event rate with intravenous immunoglobulin G is in the range of 1% to 15%, and there are approximately 100 cases of transient oliguric acute renal failure reported with the drug. The renal biopsy in one of the renal transplant patients who developed an increase in serum creatinine upon exposure to intravenous immunoglobulin G showed osmotic nephrosis of the proximal tubules [15]. In this series of 9 cases of nephrotoxicity following exposure to intravenous immunoglobulin G, 7 of the 9 cases showed vacuolization and degeneration of proximal convoluted tubule

cells. The risk factors for developing the intravenous immunoglobulin G–associated acute renal failure were a creatinine concentration of greater than 1.5 mg/dL and age over 65 years. An underlying paraproteinemia or paraproteinuria was also a risk factor [15]. Of interest is the fact that these lesions in the proximal tubule are identical to those of sucrose nephrotoxicity, which is a primary vehicle for the drug in many formulations for the drug. The mechanism of such an effect is uptake of sucrose (or any other nonmetabolizable substance such as mannitol or dextran), which leads to an increase in intracellular osmolality and subsequent cell swelling and damage. Sucrose is still used as a solubulizing agent because of lower cost, but there are other solubulizing agents, such as amino acids, on the market. Some manufacturers are also suggesting using a lower concentration of immunoglobulin G, and giving the drug slowly at a dose of 0.4 g/kg over 12 hours in an effort to reduce nephrotoxicity.

CIDOFIVIR AND ADEFOVIR

Cidofivir and adefovir are useful antiviral nucleotide analogues with activity against DNA viruses. They are used occasionally in cytomegalovirus (CMV) retinitis and against other herpes viruses, as well as HIV. Adefovir has had use in treating hepatitis B infections. With regard to cidofivir, doses greater than 5 mg/kg have been associated with acute renal failure. Renal biopsies in such cases have been characterized by proximal tubular necrosis and a dense fibrosis without an interstitial infiltrate. Other proximal tubular transport defects, such as glycosuria [16], have been seen in some patients with cidofivir nephrotoxicity.

The mechanism of cidofivir nephrotoxicity has been linked to the human organic anion transporter (hOAT). This transporter is located on the basal lateral membrane of the proximal tubule and has a key role in the excretion of metabolites, toxins, xenobiotics, and other agents with an anionic charge. The hOAT is key in the removal of salicylates, urate, and methotrexate from the blood. In addition, the hOAT also transports nucleotide analogues into the proximal convoluted tubule. Probenicid reduces the intracellular accumulation of these drugs by blocking the hOAT [16]. In one recent study in Chinese hamster ovary cells, the concentrations of adefovir and cidofovir were dramatically increased in those cells with the organic anion transporter present; the magnitude of the increase was several hundred-fold [16].

Nephrotoxicity from these 2 agents can be reduced by using probenicid at 3 g p.o. 3 hours before the dose, 2 g of probenicid 2 hours after the dose, and 1 g of probenicid 8 hours after the dose. Predose volume expansion and adequate hydration are recommended. The drug should be avoided, if at all possible, in patients with baseline serum creatinine concentrations greater than 1.5 mg/dL. One clue to the presence of adefovir toxicity is the presence of the Fanconi syndrome, with phosphaturia and hypophosphatemia reported.

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REFERENCES

1. DeBroe ME, Porter GA, Bennett WM, Verpooten GA: *Clinical Nephrotoxins: Renal Injury from Drugs and Chemicals*, Dordrecht, The Netherlands, Kluwer Academic Publishers, 2003
2. Porter GA, Palmer BF, Henrich WL: Clinical relevance, in *Clinical Nephrotoxins: Renal Injury from Drugs and Chemicals*, edited byDeBroe ME, Porter GA, Bennett WM, Verpooten GA, Dordrecht, The Netherlands, Kluwer Academic Publishers, 2003, pp 3–20
3. Dowling TC, Briglia AE, Fink JC, *et al*: Characterization of hepatic cytochrome P4503A activity in patients with end-stage renal disease. *J Clin Exp Pharmacol* 73:427–434, 2003
4. Grunfeld JP, Kleinknecht D, Droz D: Acute interstitial nephritis, in *Diseases of the Kidney* (vol II), 5th ed., edited by Schrier RW, Gottschalk CW, Boston, MA, Little, Brown, 1993, pp 1331–1353
5. Star RA: Perspectives in renal medicine. Treatment of acute renal failure. *Kidney Int* 54:1817–1831, 1998
6. Gambaro G, Perazella MA: Adverse renal effects of anti-inflammatory agents: Evaluation of selective and nonselective cyclooxygenase inhibitors. *J Intern Med* 253:643–652, 2003
7. Hao C-M, Yull F, Blackwell T, *et al*: Dehydration activates an NF-κB–driven, COX-2-dependent survival mechanism in renal medullary interstitial cells. *J Clin Invest* 106:973–982, 2000
8. Swan SK, Rudy DW, Lasseter KC, *et al*: Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet: A randomized, controlled trial. *Ann Intern Med* 133:1–9, 2000
9. Traynor TR, Smart A, Briggs JP, Schneimann J: Inhibition of macula densa-stimulated renin secretion by pharmacological blockade of cyclooxygenase-2. *Am J Physiol Renal Physiol* 277:F706–F710, 1999
10. Muscara MN, Vergnolle N, Lovren F, *et al*: Selective cyclooxygenase-2 inhibition with celecoxib elevates blood pressure and promotes leukocyte adherence. *Br J Pharm* 129:1423–1430, 2000
11. Kammerl MC, Nüsing RM, Richthammer W, *et al*: Inhibition of COX-2 counteracts the effects of diuretics in rats. *Kidney Int* 60:1684–1691, 2001
12. Chan FKL, Hung LC, Suen BY, *et al*: Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N Engl J Med* 347:2104–2110, 2002
13. Markowitz GS, Appel GB, Fine PL, *et al*: Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. *J Am Soc Nephrol* 12:1164–1172, 2001
14. Markowitz GS, Fine PL, Stack JI, *et al*: Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int* 64:281–289, 2003
15. Tsinalis D, Dickenmann M, Brunner F, *et al*: Acute renal failure in a renal allograft recipient treated with intravenous immunoglobulin. *Am J Kidney Dis* 40:667–670, 2002
16. Ho ES, Lin DC, Mendel DB, Cihlar T: Cytotoxicity of antiviral nucleotides Adefovir and Cidofovir is induced by the expression of human renal organic anion transporter 1. *J Am Soc Nephrol* 11:383–393, 2000